SYNOPSIS

Elucidating reaction mechanism of some Oxa, Thia, Aza Heterocycles and Chalcone derivatives through Computational Techniques

1. Introduction:

More than half of the all known organic compounds involve Heterocyclic compounds. The derivatives of these compounds are present in wide variety of drugs, medicinal compounds, many natural products , vitamins, biological active compounds, etc. Moreover, synthetic heterocycles have spread their therapeutic uses such as, anti-fungal, anti-microbial, anti-cancer, anti-malerial, as anti-psychotic agents, lipid peroxidation inhibitors, anti-deprsents, anti-tumor[1-4]. Literature studies show condensed derivatives like triazolo-pyrimidine and benziline having anticonvulsant, herbicidal[5-8] activities as well. Chalcones and their corresponding heterocyclic analogs are found to be valuable intermediates in organic synthesis exhibiting multiple biological activities. These have revised great attention due to their relatively simple synthesis process , structure and having a range of pharmacological activities. Various derivatives have been reported in the literature having α,β- unsaturated ketone moiety, the conjugated double bonds and the completely delocalized pi electron system on both aromatic rings.

2. Review of Literature and Development in the subject:

Synthesis, characterization and computational studies on heterocyclic compounds as well as chalcones are of interest. There has been much work done on computational studies in elucidating the reactivity of heterocycles , mechanism studies, analysis of biological activities on theoretical and experimental ground.

Density Functional Theory (DFT) describes the behavior of electrons in the molecule. This theory results in faster calculations than of Hartree-Fock (HF) calculations and computations that are more accurate. The recent development in DFT is linear scaling algorithms. The linear scaling DFT methods can be fastest than initio methods for large molecules. The quantum chemical calculations are done with DFT to test the possibility of designing new chemical system and the study of structural, electronic and

dynamical properties of compounds. The theoretical calculations were carried out by DFT.

3. Objectives of Research/ Proposed Hypothesis:

The synthesis involving plausible mechanisms are of interest to the scientists, chemists and researchers. Thus objectives of the present work include:

- Computational study of plausible mechanisms in the preparation of derivatives of nitrogen containing heterocyclic compounds.
- The study of plausible mechanisms listed in the preparation of derivatives of chalcones.
- Computational techniques used for investigation of intermediate structures and binding energies of intermediates.
- Use of Density Functional Theory (DFT) and comparison of experimental details with theoretical one.

4. Methodology:

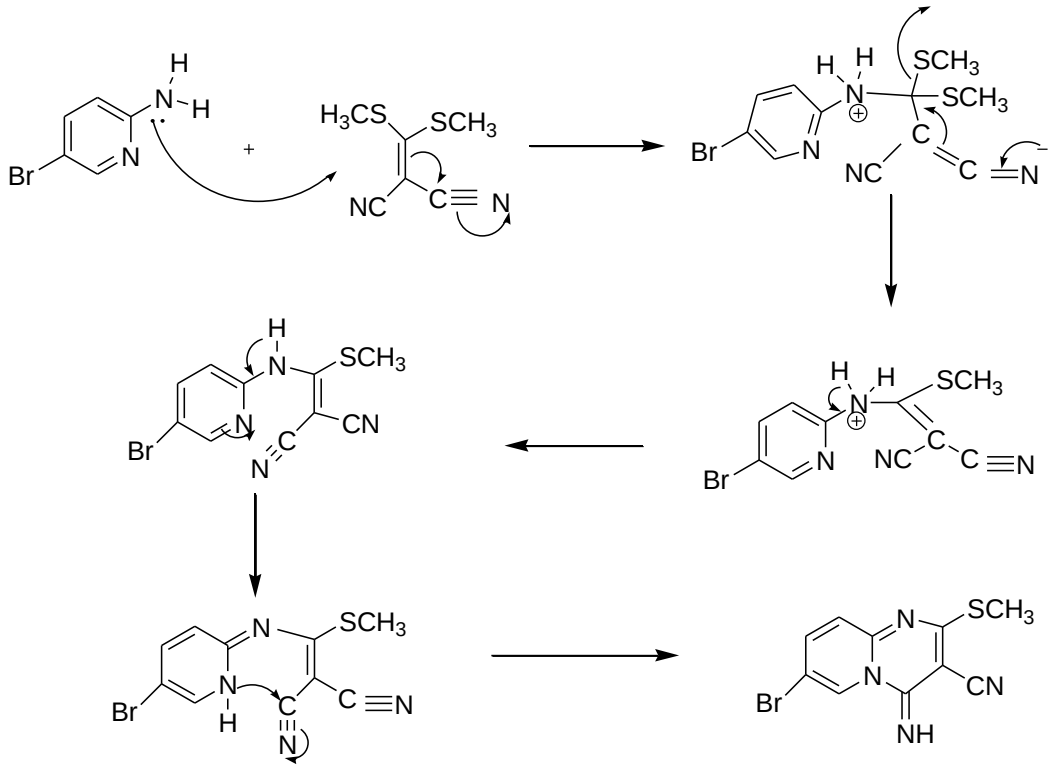
The results will be obtained using the Gaussian 09 ab initio/DFT quantum chemical simulation package [14]. All the possible conformations of all compounds will be optimized at gas phase and solvent phase using the hybrid density functional-B3LYP and Pople's split valence basis set with polarization and diffuse functions [6-311++G(d,p)] using the default integration grid and without symmetry constraints. The obtained minima will be further confirmed by the frequency calculation at the same level. Normal mode analysis and frequency assignments will be done to understand the reactivity of the reactants. The singlet geometries obtained will be subjected to TD-DFT and SAC/SAC-CI calculations to study the singlet–singlet transition. The hybrid XC functionals B3LYP and BH and HLYP, meta hybrid functionals M06-HF and M06-2X, dispersion corrected functional ωB97XD and range corrected functional LC-ωPBE and CAM-B3LYP will be used for TD-DFT calculations. The SAC-CI is restricted to singles and doubles linked operators, whereas the higher order ones are treated through unlinked operators. Four lowest excited states for each irreducible representation of each molecule are obtained. The electronic wave functions obtained at ground and excited states will be further treated with Natural Bond Orbital (NBO) analysis in order to understand the bonding interactions between reactant molecules to form products.

5. Importance of Study / Society applications:

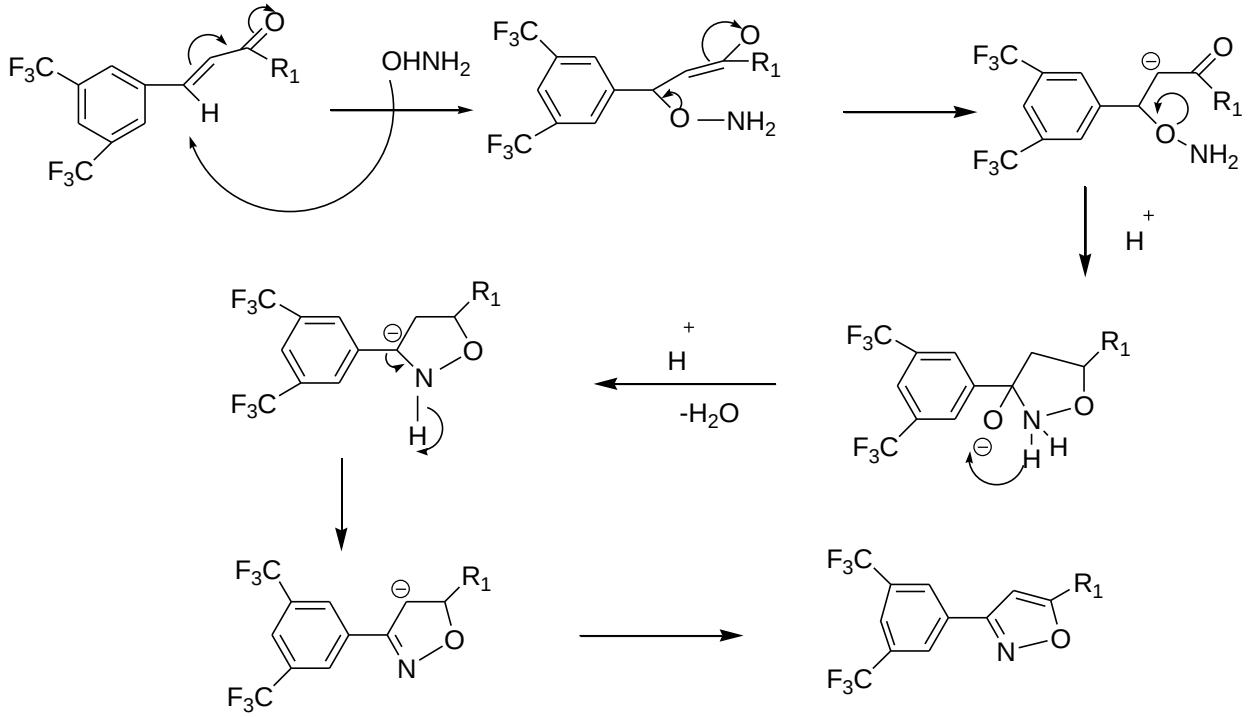
Harold D. Banks, studied computational elucidation of the extraordinary reactivity of three-membered heterocycles in nucleophilic substitution reactions [9]. Abbas et al. studied some new heterocyclic derived from 1-(biphenyl- 4-yl)-3-(furan-2-yl)prop-2-en-1-one [10]. Computational analysis for antimicrobial active pyrano[2,3- d]pyrimidine derivatives on the basis of theoretical and experimental ground was investigated by Ajmal R. Bhat and et al[11]. Sherin M El-Feky and et al. synthesized a new series of triazoles having both antifungal and anti bacterial activities[12]. Ricardo R. Ternavisk and et al. done computational study on new dimethoxy chalcone with DFT analysis[13].

6. Proposed work plan/ Formulation and Structure of Study:

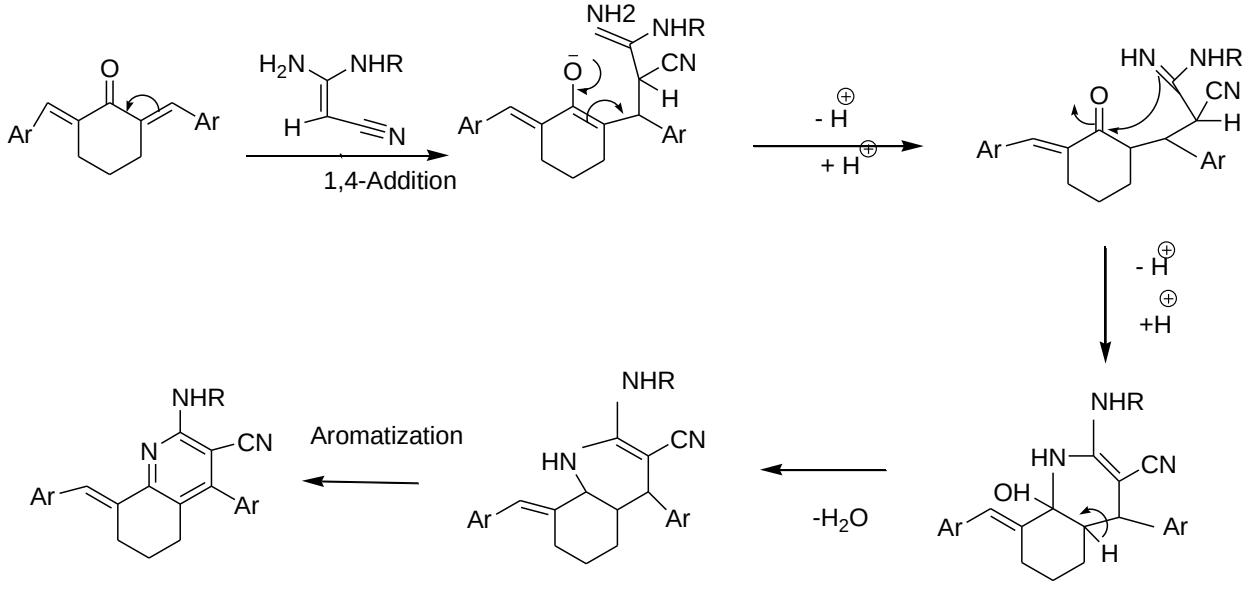
In the present work, possible mechanisms in the synthesis and investigation of heterocyclic compounds derived from oxa, thia and aza heterocycles as well as the plausible mechanism in chalcone derivatives are studied by computational techniques.



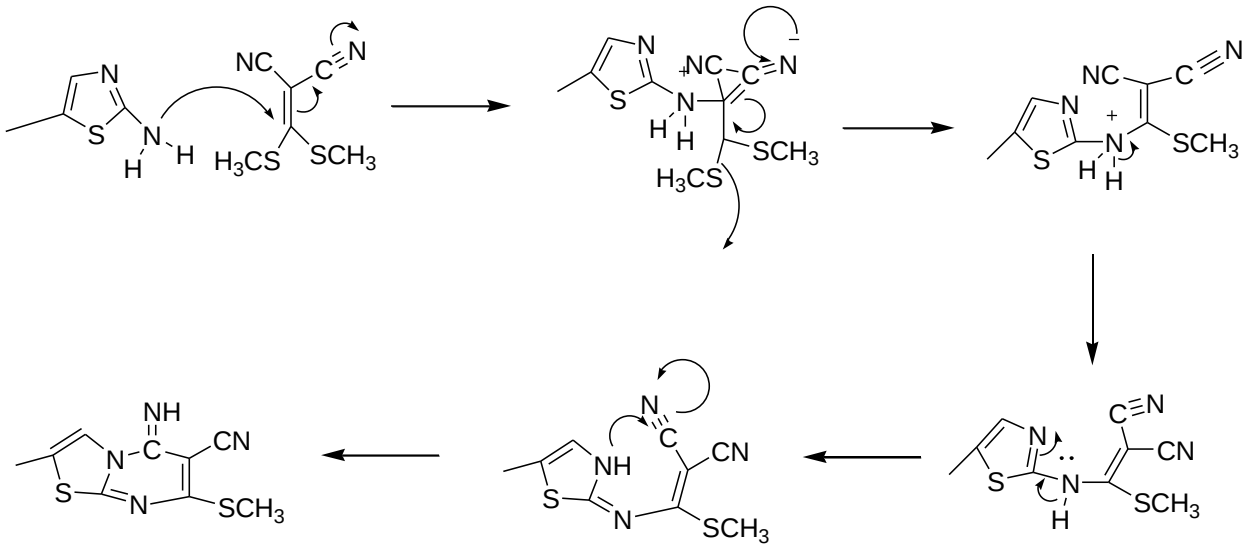
Scheme1: Possible mechanism of 7-bromo-3 cyano-4-imino-2 methylthio-4H-pyrido[1,2-a]pyrimidine



Scheme2: Possible mechanism of 3-[bis-3,5-(methyltrifluoro)phenyl]-5-phenylisoxazole.



Scheme3: Possible mechanism of bleaching earth clay catalysed reaction.



Scheme4: possible mechanism of 6- cyano-5-imino-2 methyl-7-(methylthio)-5H-thiazolo[3,2-a] pyrimidine

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